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Incidence of Female Breast Cancer among Atomic Bomb Survivors, Hiroshima and Nagasaki, 1950–1990

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An incidence survey of the Life Span Study (LSS) population found 1093 breast cancers among 1059 breast cancer cases diagnosed during 1950–1990. As in earlier breast cancer surveys of this population, a linear and statistically highly significant radiation dose response was found. In the analysis, particular attention was paid to modification of radiation dose response by age at exposure (*e*) and attained age (*a*). Dose-specific excess relative risk (ERR_{1Sv}) decreased with increasing values of *e* and *a*. A linear dose–response model analysis, with *e* and *a* as exponential age modifiers, did not conclusively discriminate between the two variables as modifiers of dose response. A modified isotonic regression approach, requiring only that ERR_{1Sv} be monotonic in age, provides a fresh perspective indicating that both *e* and *a* are important modifiers of dose response. Exposure before age 20 was associated with higher ERR_{1Sv} compared to exposure at older ages, with no evidence of consistent variation by exposure age for ages under 20. ERR_{1Sv} was observed to decline with increasing attained age, with by far the largest drop around age 35. Possible explanations for these observations are discussed, along with research approaches that might provide more information.

INTRODUCTION

This is the fifth in a series of reports (*1–4*) on female breast cancer incidence and radiation dose in the (extended) Life Span Study (LSS) (*5*) population of survivors of the atomic bombings of Hiroshima and Nagasaki, Japan, through the end of 1990.

The previous survey (*4*), covering the period October 1, 1950 through December 31, 1985, identified 807 cases, including 20 with primary cancers in opposite breasts. Dose–response analyses using the DS86 dosimetry found a linear dose response modified by age at the time of the bombings (age ATB), with the highest dose-specific excess relative risk (ERR_{1Sv}) among survivors under 20 years of age ATB and the lowest among survivors over 40 years of age ATB, and a decrease in ERR_{1Sv} with increasing attained age. It was not possible to determine whether age ATB or attained age was the more important modifier of ERR_{1Sv}. Among survivors exposed before age 20, a 13-fold ERR_{1Sv} was found for breast cancer diagnosed before age 35 and a consistent twofold ERR_{1Sv} for diagnosis after age 35. This *a posteriori* finding, based on 27 exposed, known-dose, early-onset cases, suggested the possibility of a susceptible genetic subgroup (*6*).

The focus of the present study is on clarifying the dependence of radiation-related risk on age and on critically examining the scientific basis of inferences drawn from these data.

MATERIALS AND METHODS

Case Ascertainment

Information on possible breast cancer cases among female members of the LSS-E85 sample (70,165 women in 1950) was provided by the Tumor and Tissue Registry Office of the Radiation Effects Research Foundation (RERF), which searched the LSS Tumor Registry, the local tumor and tissue registries of Hiroshima and Nagasaki, the RERF autopsy series, and the death certificate series as described in RERF guidelines (*7*). The local registries are population-based, and they routinely contribute cases from the locally resident portion of the LSS population to the LSS registry (*8*). The search also included smaller local hospitals and clinics where breast cancer is known to be treated. As in the previous series (*1–4*), special efforts were made to ascertain cases diagnosed before the Hiroshima and Nagasaki tumor registries were initiated in 1957 and 1958, respectively.

Virtually complete ascertainment of death, and of cause of death as recorded on the death certificate, is obtained by RERF for LSS sample members through the Japanese family registry system. All death certificates having ICD codes (9th revision) 174, 175, 217, 233, 238-3 and 239-3 were reviewed, and inquiries were made at the hospital at which death occurred in cases for which adequate information from other sources was not already available. In the case of deceased LSS sample members who had migrated to other parts of Japan, loans of pathological materials were requested from hospitals at which death occurred.

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Clinical and pathological data, including histological sections, were sought for all cases identified in the initial ascertainment and were reviewed without knowledge of exposure or dose. Cases accepted on the basis of available materials were assigned diagnostic certainty ratings ranging from (1) death certificate only, (2) clinical diagnosis with or without death certificate information, (3) pathological diagnosis report without review of materials by the present investigators, and (4) pathological review by the present investigators. As in previous series (*1–4*) and a binational review in 1979 (*9*), cases were classified according to the histological criteria proposed by the World Health Organization (*10*) and the Japanese Research Society for breast cancer (*11*). Cases included in the previous LSS series (*4*) were included in the present series unless new information dictated otherwise, in which case they were subjected to the same review process as cases identified for the first time. Final determination of malignancy was by the present investigators (MT and ST).

Criteria for inclusion of cases in the series of breast cancer incidence studies (*1–4*) have been somewhat different from those for the comprehensive RERF Tumor Registry report (*12*). For example, breast cancers diagnosed after diagnosis of another cancer in the same woman and cases diagnosed among women not residing in the local Hiroshima and Nagasaki tumor registry catchment areas were included in the incidence studies but not in the Tumor Registry report. Other differences are more technical, depending upon such things as whether or not a paper copy of a pathology report or clinical record was made available by the cooperating physician or medical institution for inclusion in the Tumor Registry files. In the present analysis, we examined the effects on estimated ERR_{1Sv} of inclusion of non-first-cancer cases and cases ascertained from nonlocal information sources by parallel analyses using the inclusion rule of the site-specific breast cancer incidence studies carried out heretofore (*1–4*) and one that approximates that of the comprehensive 1994 RERF Tumor Registry analysis (*12*).

Radiation Dose

The DS86 dose reconstruction algorithm (*13, 14*) was used to compute individual, neutron-weighted doses to breast tissue in sieverts. (A revised algorithm, designated DS02, is presently being implemented at RERF.) As in other recent RERF studies (e.g. *12, 15*), neutron dose in grays was assigned a weight of 10 compared to γ-ray dose. The data were organized by exposure and DS86 breast tissue dose, as follows: not in city ATB (NIC), exposed but without sufficient information for a dose estimate (UNK), and 13 intervals of weighted dose with boundaries at 0, 5, 20, 50, 100, 200, 500 and 750 mSv and at 1, 1.5, 2, 3, 4 and 6.2 Sv.

Statistical Analysis

The AMFIT algorithm (*17*) for unconditional, Poisson-model, maximum-likelihood regression of grouped survival data was used to test for the existence of dose-related ascertainment bias to estimate the possible dependence of risk on radiation dose and to evaluate the variation of ERR_{1Sv} by city, age ATB, time after exposure, and attained age. Numbers of woman-years (WY) of observation for risk were accumulated through the date of diagnosis of (first) breast cancer for cases and to the date of death or December 31, 1990 for non-cases. Numbers of cases and WY were obtained for cells defined by exposure status and intervals of dose as described in the previous paragraph, city, age ATB (5-year intervals to age 70, plus 70 and older), attained age (5-year intervals from age 5 through 84, plus 85 and older), and calendar year (1950–1955, 1956–1957, 1958–1960, 5-year intervals from 1961 through 1985, 1986–1987, and 1988–1990. The 5-year intervals 1956–1960 and 1986–1990 were split because the tumor registries began in 1958 and the 1994 comprehensive tumor registry incidence report (*12*) covered 1958–1987. The analysis of rates among the exposed with dose estimates with respect to average weighted breast tissue dose in each cell was adjusted by the method of Pierce *et al.* (*16*) to correct for negative bias in estimated linear-model excess risk per unit dose, induced by random errors in individual dose estimates. The bias correction involves a downward adjustment of the mean dose in each cell and a consequent increase in estimated risk per sievert.

Excess relative risk (ERR) was estimated using stratified relative risk models, in which a saturated log-linear model was used to estimate baseline (zero-dose) risk in non-empty strata defined by the two cities, 15 age-ATB intervals, and 17 attained-age intervals. Migration of LSS cohort members from Hiroshima and Nagasaki to other parts of Japan is known to have occurred differentially by city, sex and age ATB, but it did not differ by radiation dose (*12*); thus no adjustment for migration was deemed necessary for analyses of dose-related ERR.

Dose–response models presented here are expressed in terms of excess relative risk:

$$\mathrm{ERR}(D_L, e, a) = f(D_L) \times \mathrm{ERR}_{1Sv}(e, a), \tag{1}$$

where D_L is the neutron-weighted breast tissue dose in sieverts, truncated at zero for t less than the estimated minimum latent period L, and $f(D_L) = D_L$ or $D_L \times (1 + \theta D_L)$ for linear and linear-quadratic dose response, respectively, where θ is an unknown parameter. $\mathrm{ERR}_{1Sv}(e, a)$ expresses excess relative risk at 1 Sv as a function of exposure age e and attained age a.

The usual linear model used in Thompson *et al.* (*12*) and other presentations defines

$$\mathrm{ERR}_{1Sv}(e, a, \text{standard}) = \exp[\ln(\alpha) + \ln(\beta) \times (e - 25) + \gamma \times \ln(a/50)], \tag{2}$$

where α, β, and γ are unknown parameters. Thus $\alpha = \mathrm{ERR}_{1Sv}$ for women age 50 who were exposed at age 25. A different specification of $\mathrm{ERR}_{1Sv}(e, a)$, motivated by the isotonic regression approach of Barlow *et al.* (*18*), was used here as a descriptive and exploratory device for examining the functional form of the dependence of ERR_{1Sv} on age ATB and attained age, under the constraint that ERR_{1Sv} be monotonic in e and a. Computation began with separate estimates of ERR_{1Sv} for 12 basic intervals of age ATB and of attained age:

$$\mathrm{ERR}_{1Sv}(e, \text{age ATB isotonic}) = \sum_{i=1}^{12} \delta_i \times I_i(e), \tag{3}$$

$$\mathrm{ERR}_{1Sv}(a, \text{attained age isotonic}) = \sum_{i=1}^{12} \varepsilon_i \times J_i(a), \tag{4}$$

where $\{\delta_i\}$ and $\{\varepsilon_j\}$ are indexed arrays of unknown parameters constrained to be monotonic in i and j, respectively, and the indicator functions $\{I_i\}$ and $\{J_j\}$ correspond to intervals of age ATB and attained age, respectively. The monotonicity constraint (e.g. monotone non-increasing) requires that parameters corresponding to adjacent age intervals be either identical in value (and estimated from pooled interval data) or differ in the prescribed direction. The estimation process was an iterative one, proceeding from lower to higher age intervals and repeating each time two adjacent intervals were combined, and ending when monotonicity was achieved (*18*). The two-dimensional analogue of this process, based on the intersections of intervals in e and a, yielded a bivariate isotonic regression monotonic in both e and a, with parameters $\eta_{i,j}$ and indicator functions $K_{i,j}(e, a)$:

$$\mathrm{ERR}_{1Sv}(e, a, \text{isotonic}) = \sum \eta_{i,j} K_{i,j}(e, a) \tag{5}$$

Goodness of fit was evaluated in terms of deviance (−2 times the sum over cells of the natural logarithm of the fitted likelihood function, plus a data-dependent constant) and, for hierarchical models defined by fixing the values of certain parameters at null values (zero or one, as appropriate), by deviance differences asymptotically distributed as χ^2 with known degrees of freedom. All reported P values are two-tailed, based on likelihood ratio or score tests. Point estimates are presented with two-sided, equi-tailed, 90% likelihood profile confidence intervals. Deviance was also used less formally to evaluate fit for isotonic regression analyses.

The dose response for double primary breast cancer was analyzed by Poisson regression for incidence and by binomial-model maximum likelihood regression (the GMBO algorithm) (*17, 19*) for the proportion of double primary breast cancer cases among all cases.

RESULTS

Case Ascertainment

In all, 1059 breast cancer cases, 34 of them double primaries, were included in the series. Thirty-six of the breast cancer cases were diagnosed after, or at the same time as, cancers of other organ sites, and notification for another 47 cases was on the basis of non-local information. Thus 1059 breast cancer cases (776 exposed with DS86 dose estimates) were identified under the inclusion rule used for previous breast cancer incidence series (*1–4*), and 976 (714) were identified under the more restrictive rule approximating that of the comprehensive tumor registry incidence study (*12*). The total also included 34 cases of invasive intra-ductal carcinoma, two of which were diagnosed before age 35, and two breast lymphomas, both of them diagnosed after age 50 and both low-dose. These cases also were not used in the incidence analyses of Thompson *et al.* (*12*) or in a more recent parallel analysis comparing breast cancer risks in the LSS and several other radiation-exposed cohorts (*20*). The distributions of cases by calendar year, age ATB, attained age, exposure status, and estimated radiation dose were virtually identical for the two LSS case-inclusion rules. All analyses were done in parallel using the two inclusion rules, and no substantive differences were found except as mentioned below. Thus only the results for the less restricted collection of cases are presented in any detail.

Of the 1093 total breast cancers, 893 were accepted based on pathology review by the present investigators, 88 on pathology reports by other pathologists, 55 on clinical information, and 57 on death certificate information only. There was no association between the basis of acceptance and radiation dose [nonhomogeneity $\chi^2 = 3.4$ with 15 degrees of freedom (df), $P = 0.998$; data not shown]. Review of medical histories of the 36 second-cancer cases suggested that none of the breast cancers were likely to have been causally related to treatment for the first cancer.

Ascertainment by Age ATB, Age at Diagnosis, and Calendar Time

The correlation between age ATB and age at diagnosis among individual breast cancers was 0.71. Age at diagnosis ranged from 24 to 98, and for fixed exposure age e, age at diagnosis was necessarily between $e + 5$ in 1950 and $e + 45$ in 1990. Numbers of cases increased since the previous report by 82, 37, 31, 25, 12 and 2% for women exposed at ages 0–9, 10–19, 20–29, 30–39, 40–49 and 50 or older, respectively, and 55% of cancers diagnosed during 1986–1990 occurred among women under 20 years of age ATB.

Preliminary Dose–Response Analysis

Estimates of dose-specific relative risk for 1950–1990 are plotted, with 90% confidence limits, in Fig. 1 for the exposed cohort members by dose interval and for subjects in the NIC and unknown dose groups. Of the 1059 cases in the series, 190 occurred among the NIC and 93 among the unknown dose, and the remaining 776 cases had estimated breast tissue doses between zero and 6 Sv. Breast cancer incidence was nonsignificantly lower in the NIC group than in the zero-dose, exposed group. It was significantly elevated in the unknown dose group to a level consistent with an average dose of about 0.5 Sv. The fitted dose response for the exposed, known-dose women is also plotted in Fig. 1. Estimated ERR_{1Sv} was 1.68 with 90% confidence limits 1.31–2.10.

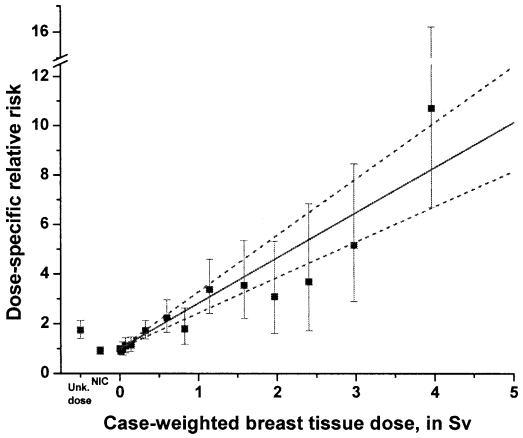

FIG. 1. Estimated relative risk of breast cancer, with 90% confidence limits, by exposure status and radiation dose, with fitted linear dose response for exposed subjects with dose estimates. All ages combined.

Minimum Latent Period

The minimum time from exposure until the appearance of a radiation-related excess risk was estimated by applying different latency assumptions to the simple linear dose–response analyses described in the preceding paragraph. The comparison was constrained by the calendar-time divisions of the data set, beginning October 1, 1950, 5 years after the bombings, and January 1 of 1956, 1958, 1961, 1966, etc. for subsequent intervals. Thus a minimum latency of 15 years, for example, was approximated by setting dose = 0 for cells corresponding to 1950–1955, 1956–1957, and 1958–1960. Compared to an assumed minimum latent period of 5 years or less (ending on or before October 1, 1950), a deviance drop of 1.6 was found for 10 years (to January 1, 1956), 7.9 for 12 years (to 1958), and 6.0 for 15 years (to 1961), and a deviance increase of 7.3 was found for 20 years (to 1966). That is, the best fit to the data (indicated by a larger, positive deviance drop) corresponded to a minimum latent period of about 12 years. This minimum latent period has been assumed in all analyses presented subsequently.

Linearity of Dose Response and Stability of Linear Estimates at Low Doses

With an assumed 12-year minimum latent period, the estimated ERR_{1Sv} was 1.83 (1.43–2.28) for combined cities,

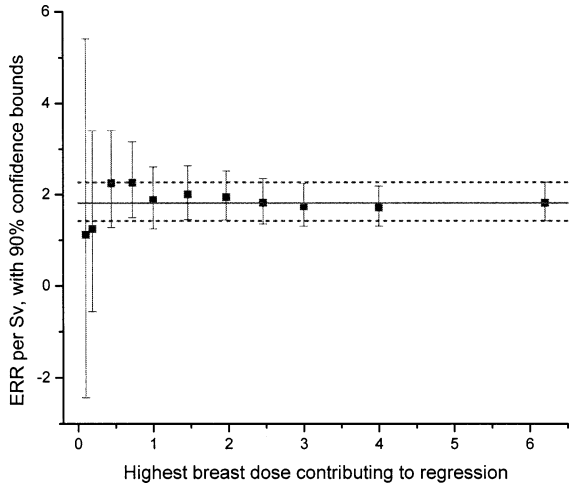

FIG. 2. All-age linear regression estimates of ERR_{1Sv}, assuming a 12-year minimum latent period, with dose-specific data trimmed from the right. The right-most point corresponds to a dose–response analysis over the full dose range, the next point to the left to doses under 4 Sv, the next to doses under 3 Sv, and so on.

ages, and calendar year intervals compared to 1.68 for an assumed 5-year latency, reflecting the relative lack of a dose response before 1958. There was no evidence of departure from linearity: The estimated parameter θ in the linear-quadratic model, where ERR is proportional to $D_L \times (1 + \theta D_L)$, was 0.0004 (−0.11 to 0.22). The upper limit on θ corresponds to a lower, one-sided 95% confidence limit of 1/0.22 = 4.5 Sv for the ''crossover dose'' at which the linear and quadratic components of radiation-related risk are equal.

Trimming high-dose observations from the data set did not markedly affect the linear model estimate, as shown in Fig. 2. The plotted points and confidence bars represent ERR_{1Sv} estimates computed over ranges of breast dose from zero to (reading from right to left) 6.2, 4, 3, 2.5, 2, 1.5 and 1 Sv, and 750, 500, 200 and 100 mSv. As the dose-specific data were trimmed from the right, the confidence limits for estimated ERR_{1Sv} became wider, reflecting loss of informative high-dose data. However, the point estimates did not go outside the original confidence limits, 1.43–2.28, until, after the data were restricted to doses under 200 mSv, the confidence limits on estimated risk became very wide. These results demonstrate that the linear model estimate is highly consistent with data at low to moderate doses.

Dose–Response Analysis with Modification by City and Age

Standard model (2) analyses of dose response found no evidence that dose-specific ERR varied by city (analysis not shown); however, according to analyses summarized in Table 1, ERR_{1Sv} decreased significantly with either age ATB or attained age considered separately. Similarly to earlier breast cancer series (*4*), it is difficult to separate the modifying effects of the two correlated age variables.

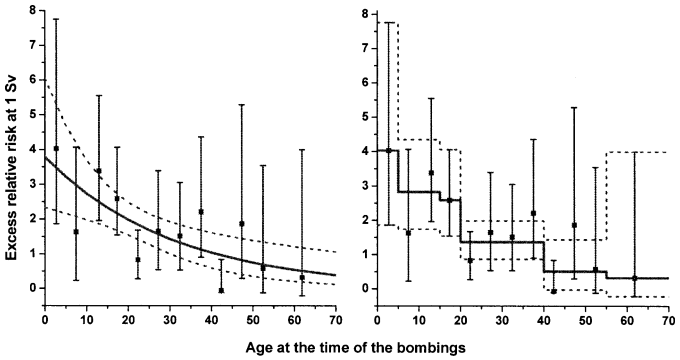

FIG. 3. Estimated excess relative risk per Sv with 90% confidence limits, by 5-year intervals of age ATB, *e.* The panels show a fitted exponential function on the left, $ERR_{1Sv} = a \times \beta^{e-25}$, and an isotonic regression on the right constrained only to be monotone non-decreasing in *e.*

The left-hand panels of Figs. 3 and 4 show the variation in estimated ERR at 1 Sv by interval of age ATB and attained age, respectively. Separate regression estimates, with no modifying factors, were computed for age-ATB intervals 0–4, . . . , 50–59 and ≥60 and for attained ages <35, 35–39, . . . , 80–84 and ≥85. They also show fitted exponential models (model 2) corresponding to parameters estimates in Table 1, assuming no dependence on attained age ($\gamma = 0$) in the case of Fig. 3 or on age ATB in the case of Fig. 4 ($\beta = 1$). The left-hand panel of Fig. 4 suggests that expressing variation in ERR_{1Sv} as a negative power function of attained age may not fit the dose–response data particularly well. The extremely high value of ERR_{1Sv} for attained age under 35, which has been suggested as a possible indicator of a radiosensitive genetic subset of the LSS population (*6*), is a clear outlier from the fitted function.

Isotonic Regression

An isotonic regression analysis (model 3) of the data of the left-hand panel of Fig. 3 is shown in the right-hand panel of the same figure and in Table 2. The analysis indicates that estimated ERR_{1Sv} declined with age ATB, with

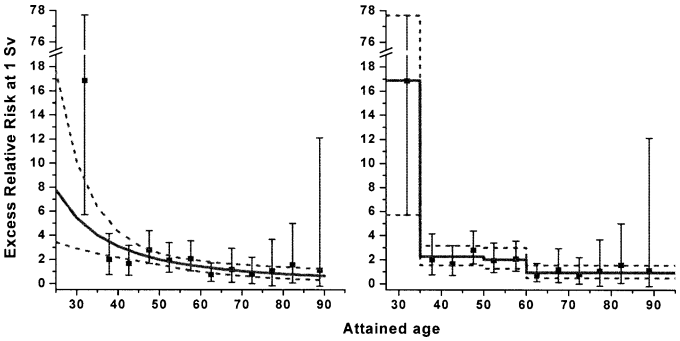

FIG. 4. Estimated excess relative risk per Sv with 90% confidence limits, by 5-year intervals of attained age. The panels show a fitted exponential function on the left, $ERR_{1Sv} = \alpha \times (a/50)^{\gamma}$, and an isotonic regression on the right constrained only to be monotone non-decreasing in *a.*

TABLE 1
Linear Dose–Response Analyses with Modification by Age ATB and Attained Age, all Exposed Cases

Parameter	Parameter estimate	90% confidence limits	*P* value for modifying variable	Deviance drop (degrees of freedom) *P* value
α (dose)	1.81	1.42, 2.26		0
β (exposure age)	1[a]	—	—	—
γ (attained age)	0[a]	—	—	
α	1.66	1.24, 2.12		8.68
β	0.965	0.943, 0.985	0.0032	(1)
γ	0[a]	—	—	0.003
α	2.01	1.56, 2.52		6.89
β	1[a]	—	—	(1)
γ	−1.69	2.83, −0.628	0.0087	0.009
α	1.75	1.29, 2.28		9.44
β	0.974	0.947, 1.001	0.11	(2)
γ	−0.777	−2.25, 0.710	0.38	0.009

Note. Standard model: $ERR_{1Sv}(e,a;\text{standard}) = \alpha \times \beta^{e-25} \times ({}^{a}/_{50})^{\gamma}$, where e is age ATB, a is attained age, and α, β and γ are unknown parameters. Note that α corresponds to ERR_{1Sv} for $e = 25$ and $a = 50$ when neither β nor γ is fixed.

[a] Fixed parameter value corresponding to no influence of age ATB ($\beta = 1$) or attained age ($\gamma = 0$).

the major drops, relative to the confidence bounds, at around 20 and 40 years of age ATB. Table 3 and the right-hand panel of Fig. 4 illustrate isotonic regression analyses with respect to attained age (model 4). The decrease in ERR_{1Sv} with increasing attained age at diagnosis was precipitous at around age 35, followed by a relatively gradual decrease at older ages. Finally, Fig. 5 shows separate isotonic regressions on attained age (model 4) for women exposed at ages 0–19, 20–39 and 40 or older (panels a, b and c, respectively).

A bivariate isotonic regression analysis (model 5) of age-specific ERR_{1Sv} on age ATB and attained age is summarized in Fig. 6. The deviance drop for the bivariate regression, compared to a model in which ERR_{1Sv} is constant in age ATB and attained age, was 21.17 (6 *df*). This compares with deviance drops of 13.38 (5 *df*) and 16.53 (3 *df*) for the univariate regressions of Tables 2 and 3, respectively. Neither univariate isotonic regression model is a special case of the fitted bivariate model, and it is not obvious how to compare the bivariate and univariate models.

The major divisions of the analysis of Fig. 6 are those of the three panels of Fig. 5: ages 20 and 40 ATB, and attained ages 35 and 60 for women under 20 and 20–39 ATB, respectively.

TABLE 2
Example of Isotonic Regression

Age ATB	Breast cancer cases	Age-specific ERR at 1 Sv (90% confidence limits)	
		By 5-year interval	Isotonic regression
0–4	53	3.94 (1.82–7.60)	3.94 (1.82–7.60)
5–9	46	1.65 (0.24–4.11)	2.77 (1.70–4.26)
10–14	83	3.27 (1.89–5.35)	
15–19	125	2.66 (1.59–4.15)	2.65 (1.59–4.15)
20–24	98	0.86 (0.29–1.72)	
25–29	80	1.53 (0.49–3.18)	1.33 (0.85–1.94)
30–34	81	1.46 (0.51–2.95)	
35–39	71	2.08 (0.84–4.08)	
40–44	55	−0.09 (<0–0.76)	
45–49	37	2.27 (0.43–6.21)	0.54 (−0.003–1.42)
50–54	24	0.55 (<0–3.34)	
55–82	23	0.76 (<0–5.38)	
Deviance difference (degrees of freedom)		0	6.890 (7)

Notes. Linear-model regression estimates of ERR_{1Sv} by 5-year interval of age ATB (column 3), and constrained to be a monotonic non-increasing function of attained age (column 4; see right-hand panel of Fig. 3). The deviance difference between the models of columns 3 and 4 suggests that the isotonic model fits reasonably well.

TABLE 3
Example of Isotonic Regression

Attained age in years	Breast cancer cases	Age-specific ERR at 1 Sv (90% confidence limits)	
		By 5-year interval	Isotonic regression
20–34	28	16.78 (5.72–76.2)	16.82 (5.74–76.2)
35–39	45	1.98 (0.75–4.11)	
40–44	84	1.64 (0.69–3.11)	2.24 (1.54–3.13)
45–49	122	2.81 (1.68–4.39)	
50–54	102	1.82 (0.89–3.17)	1.98 (1.24–2.94)
55–59	110	2.15 (1.10–3.69)	
60–64	83	0.75 (0.17–1.70)	
64–69	63	1.09 (0.07–2.77)	
70–74	64	0.82 (0.003–2.25)	0.93 (0.46–1.53)
75–79	37	1.21 (−0.13–4.03)	
80–84	27	1.50 (0.04–4.83)	
85+	11	0.92 (<0–11.58)	
Deviance difference (degrees of freedom)		0	1.816 (8)

Notes. Linear-model regression estimates of ERR_{1Sv} by 5-year intervals of attained age (column 3) and constrained to be a monotonic non-increasing function of attained age (column 4; see right-hand panel of Fig. 4). The deviance difference between the models of columns 3 and 4 suggests that the isotonic model fits reasonably well.

Comparison of Exponential and Isotonic Regression Models

Models (2) and (5) were compared by adding exponential dose–response modifier terms in age ATB and log(age/50) to the final bivariate isotonic regression model (5) corresponding to Fig. 6:

$$\mathrm{ERR}_{1\mathrm{Sv}}(e, a, \text{modified isotonic}) = \sum\sum \zeta_{i,j} K_{i,j}(e, a) \times \beta^{e-25} \times (a/50)^{\gamma} \qquad (6)$$

(analysis not shown). Adding these terms did not improve the fit significantly over the bivariate isotonic model ($P = 0.13$), although adding attained age (e) alone produced a marginal improvement in fit ($P = 0.054$). However, the estimated parameter values β and γ were greater than one and positive, respectively, which suggests that the step functions in Fig. 6 might fit a little better if each of the steps, instead of being flat, were not isotonic but instead sloped slightly upward toward the edges. On the other hand, adding the isotonic regression substantially improved fit over the conventional model (2). The deviance reduction from adding the step functions of Fig. 6 to the conventional model (1) was 18.5 with 6 degrees of freedom (analysis not shown).

A summary is given in Table 5 of the effect of adding an indicator variable, for the event "attained age <35", to the full-model, formula (1) analyses of Table 1:

$$\mathrm{ERR}_{1\mathrm{Sv}}(e, a, \text{standard}) = \alpha \times \beta^{e-25} \times (a/50)^{\gamma} \times \zeta^{J(a)}, \qquad (7)$$

where e is age ATB, a is attained age, $J(a) = 1$ if $a < 35$ and $= 0$ otherwise, and α, β, γ and ζ are unknown parameters. Adding the indicator variable $J(a)$ to the model yielded a statistically significant deviance drop of 5.7 ($P = 0.007$) (Table 5). With this addition, furthermore, it became possible to distinguish, using this model, between the modifying effects of age ATB and of attained age as it might apply *after* age 35. Removal of both age ATB (e) and attained age (a) from the full model accounted for a deviance increase of 5.92 with 2 *df* ($P = 0.052$; analysis not shown). Removal of age ATB from the full model accounted for a

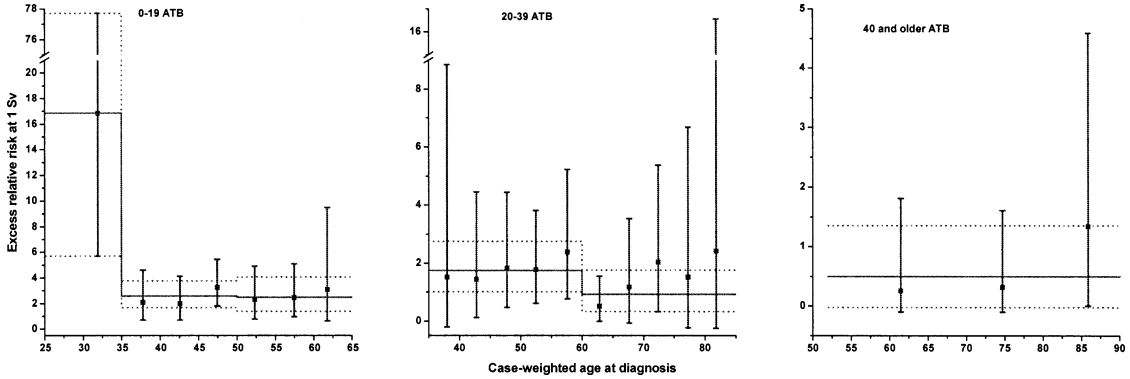

FIG. 5. Isotonic regressions of ERR_{1Sv} on attained age for different intervals of age ATB.

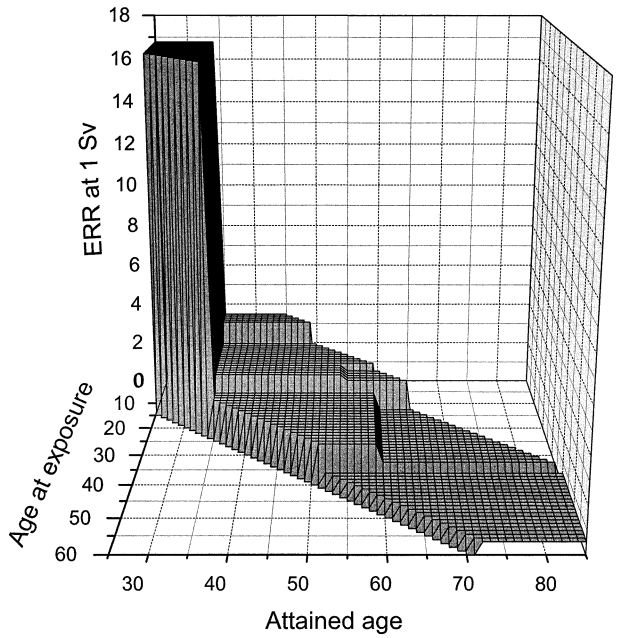

FIG. 6. Bivariate isotonic regression: ERR_{1Sv} as a monotonic, non-decreasing function of exposure age and attained age. All breast cancer cases. Heights of steps in ERR_{1Sv}, with 90% confidence limits, are (from highest to lowest): 17 (5.7–76.), 3.5 (1.4–7.2), 2.5 (1.6–3.6), 2.2 (0.95–4.2), 1.7 (0.99–2.7), 0.90 (0.31–1.7), and 0.54 (0.00–1.4).

statistically significant deviance increase of 4.18 ($P = 0.041$), while removal of attained age from the full model corresponded to a deviance increase of 0.21 ($P > 0.5$) (Table 4). Finally, adding age ATB to a model dependent only on radiation dose and $J(a)$ resulted in a statistically significant drop in deviance ($P = 0.017$), whereas adding attained age gave a nonsignificant deviance drop ($P = 0.19$). This analysis supports the interpretation that dependence of radiation-related risk on attained age mainly reflects the early-onset risk phenomenon, but that, even after adjustment for this phenomenon, dependence on exposure age remains important.

Comparison with Other RERF Breast Cancer Series

As mentioned under *Case Ascertainment*, the above analyses are based on 776 breast cancer cases (including 28 early-onset cases) among exposed women with radiation dose estimates. Similar results were obtained in parallel analyses based on a subset of 714 cases (23 of them early-onset) reported to the LSS Tumor Registry on the basis of locally available information, and excluding breast cancers diagnosed after prior diagnosis of another type of cancer. In particular, the model (7) analysis for the subset, shown in Table 4, produced essentially the same results as those based on the larger number of cases, although exposure age did not significantly improve fit as a dose–response modi-

TABLE 4
Linear Dose–Response Analyses with Modification by Age ATB and Attained Age, for Different Case Series and Case Inclusion Rules

Case series	Parameter (variable)	Parameter estimate	90% confidence limits	*P* values: When all other parameters included in model	*P* values: Given null value for γ ($\gamma = 0$)	*P* values: Given null value for β ($\beta = 1$)
This study: all cases (776 cases, 28 early-onset)	α (dose)	1.52	1.08, 2.03			
	β (exposure age)	0.97	0.94, 0.99	0.041	0.017	—
	γ (attained age)	0.46	−1.19, 2.18	>0.50	—	0.19
	ζ (age at diagnosis <35)	8.53	2.30, 47.6	0.007	0.005	0.0018
This study: first primary cases, locally available data (714 cases, 23 early-onset)	α (dose)	1.57	1.11, 2.11			
	β (exposure age)	0.97	0.94, 1.00	0.15	0.044	—
	γ (attained age)	−0.02	−1.78, 1.80	>0.50	—	0.16
	ζ (age at diagnosis <35)	9.32	2.15, 90.8	0.012	0.004	0.0024
Previous study in this series (*4*), 1950–1985: (591 cases, 28 early-onset)	α (dose)	1.32[a]	0.92, 1.80		—	
	β (exposure age)	0.97	0.93, 1.00	0.14	0.034	—
	γ (attained age)	0.19	−1.87, 2.38	>0.50	—	0.13
	ζ (age at diagnosis <35)	7.24	1.83, 42.8	0.018	0.009	0.035
1958–1987 LSS Tumor Registry report (*12, 21*) (537 cases, 20 early-onset)	α (dose)	1.41[a]	0.96, 1.94			
	β (exposure age)	0.97	0.94, 1.01	0.23	0.021	—
	γ (attained age)	−0.74	−2.86, 1.40	>0.50	—	0.039
	ζ (age at diagnosis <35)	4.16	0.99, 21.1	0.10	0.027	0.16
LSS Tumor Registry data, 1958–1993, from pooled analysis (*20*) (707 cases, 20 early-onset)	α (dose)	1.75	1.27, 2.31			
	β (exposure age)	0.98	0.95, 1.01	0.22	0.066	—
	γ (attained age)	−0.26	−1.82, 1.33	>0.50	—	0.16
	ζ (age at diagnosis <35)	7.93	1.76, 54.6	0.024	0.009	0.037

Notes. Modified standard model: ERR_{1Sv} (e,a: standard) $= \alpha \times \beta^{e-25} \times ({}^{a}/50)\gamma \times \zeta^{J(a)}$, where e is age ATB, a is attained age, $J(a) = 1$ if $a < 35$ and $= 0$ otherwise, and α, β, γ and ζ are unknown parameters. Note that α corresponds to ERR_{1Sv} for $e = 25$ and $a = 50$.

[a] Based, as in the original publications, on DS86 dose uncorrected for random error.

TABLE 5
Binomial, Linear-Model Analysis of Proportion of Double Primary Cases by Age ATB

Age ATB	Exposed cases with DS86 dose	Double primary cases (%)	Excess relative risk (odds ratio) per Sv, adjusted for age ATB	*P* value for dose response
Total	776	26 (3.4%)	0.54 (−0.003, 1.75)	0.14
<20 ATB	307	15 (4.9%)	1.11 (0.13, 4.05)	0.034
≥20 ATB	469	11 (2.3%)	<0 (<0, 0.82)	>0.50

fier in the presence of both attained age and the early-onset contrast.

Table 4 also shows the results of corresponding analyses of data from three other LSS series: 591 incident breast cancer cases diagnosed during 1950–1985 (*4*), 537 incident breast cancer cases from the 1958–1987 LSS Tumor Registry report (*12*), including 8 high-dose cases not included in the original analysis restricted to subjects with estimated doses under 4 Gy, and 707 diagnosed between 1958 and 1993 which were included in a pooled analysis of breast cancer incidence data from a number of studies (*20*). The present series and the 1950–1985 series include 28 exposed, early-onset cases; the other two data sets contain 20 early-onset cases. In all analyses, exposure age and diagnosis before age 35 contributed significantly (or nearly significantly) to a model containing only those two modifiers and explained essentially all the variation associated with modification of dose response by age.

Risk of Double Primary Breast Cancer

Thirty-four of the 1059 breast cancer cases, and 27 of the 767 cases among the survivors with DS86 dose estimates, involved cancers of opposite breasts diagnosed at the same time or separated by months or years. The simple, linear dose–response coefficient for double primary breast cancer, stratified by city, exposure age, and attained age, was $ERR_{1Sv} = 4.00$, with 90% confidence limits 1.42–9.36 (analysis not shown). Among cases, the proportion of double primary cases increased by 0.54 (−0.003–1.75) per sievert ($P = 0.14$) (Table 5). Of the 307 exposed cases under 20 years of age ATB with dose estimates, 15 (4.9%) developed primary cancers in both breasts, compared to 11 of 469 cases (2.3%) 20 or older ATB. Among cases less than 20 ATB the proportion of such cases increased significantly with increasing dose ($ERR_{1Sv} = 1.11$, 0.13–4.05, $P = 0.034$), while among cases 20 or older ATB the proportion did not increase with dose (Table 5).

In 4 of 26 (15%) exposed double primary cases with dose estimates, the first primary occurred before age 35; all 4 early-onset cases were under 20 ATB. However, the mean radiation dose was only 0.3 Sv among the 4 early-onset, double primary cases compared to 1.6 Sv for the 11 later-onset cases. Thus there may be no obvious connection between the two dose-related phenomena of early-onset and double primary breast cancer risk.

DISCUSSION

Our analysis showed that inferences in terms of dose-related relative risk did not depend heavily on which breast cancer case inclusion rule of the two considered here was used. This finding supports the inference from Adult Health Study statistics (*12*) that migration of LSS population members from the Hiroshima and Nagasaki areas (the catchment area for the RERF Tumor Registry), while dependent upon birth cohort and sex, has not depended upon radiation dose from the bombings and is not a source of bias for estimates of radiation-related relative risk. For estimates of radiation-related absolute risk, on the other hand, the more restrictive inclusion rule is to be preferred because it corresponds to the PY denominator used for analyses of RERF Tumor Registry data (*12*).

The present data strengthen the earlier finding (*4*) that radiation-related breast cancer risk has been substantially higher among women exposed during childhood or adolescence than among women exposed at older ages. The general pattern, that of a decline in dose-specific ERR with increasing age at exposure, has been observed in a number of different studies. For an enlightening summary, see ref. (*22*), pages 137 and 155, and ref. (*20*). Our data suggest that the dose-specific ERR for breast cancer is high after exposure before age 20 but not that it is especially high for exposure at any particular age or age range within that interval. The data provide no consistent support for the hypothesis that sensitivity to radiation-related breast cancer is especially high for exposure around, or after, menarche or breast budding compared to other young ages, as suggested by Korenman (*23*) and Russo (*24*), or in the second compared to the first decade of life. Rather, data from the present study and the Rochester, NY study of breast cancer risk in patients treated in infancy for enlarged thymus (*25*) indicate that irradiation of breast tissue precursor cells is associated with excess breast cancer risk comparable to that associated with exposure at somewhat older ages. This inference is seemingly contradicted by the results of a Swedish study of women treated in infancy, mainly with ^{226}Ra applicators, for skin hemangioma (*26*) and a U.S. study of women treated as children and adolescents for Hodgkin's disease (*27*). The Swedish study found an ERR per Gy of only 0.35 (95% CI 0.18–0.59), while the latter study found a significantly greater breast cancer risk among women treated for Hodgkin's disease at 10–16 years of age (16

cases) compared to women treated at ages younger than 10 (1 case) (RR = 6.7, 95% CI 1.2–28.6). Median follow-up in the Hodgkin's disease study was only 11 years (range 0.1–37), and the patients treated before age 10 may still have been too young to manifest a radiation-related risk. In the LSS series, the excess risk associated with exposure at ages under 10 was not apparent until follow-up exceeded 30 years (*2, 3*). In the hemangioma study, however, the mean follow-up was 45 years (range 1–74). The study authors suggested that exposure at low dose rates from the radium applicator may have had a reduced carcinogenic effect (*26*).

The ''early-onset'' phenomenon was not observed among women exposed as adolescents to multiple chest fluoroscopy examinations in Massachusetts tuberculosis sanatoria (*29*), but something similar was seen among female Hodgkin's disease survivors treated in two Dutch cancer centers between 1966 and 1986 (*30*). In the latter study, relative risk among women treated at 20 years of age and younger was 61.5, with 95% confidence limits 25–127, for diagnosis before age 40, compared to an RR of 5.4 (0.7–19.5) for diagnosis at ages 40–49.

Our analysis of double primary breast cancer cases by age ATB (Table 5) suggests that the proportion among women under 20 years of age ATB is dependent on dose, whereas that among women exposed at older ages is not. This is another possible indication of increased sensitivity at young ages, but may it not be connected to the early-onset phenomenon.

A important question for radiation protection policy is whether higher relative risks have been observed among women <20 ATB because they were exposed at more sensitive ages or because they were observed for risk at younger ages. In the present series, age at exposure and attained age are highly correlated even after 40 years of follow-up. Kellerer and Barclay (*28*) observed that estimates of lifetime risk of radiation-related cancer after exposure at young ages can differ by a factor of 4 or more, depending upon whether ERR_{1Sv} varies mainly by exposure age or attained age. The problem is that the two models, with such different implications for radiation protection, can fit the same data equally well. Our model (2) analysis (Table 1) did not discriminate between attained age and exposure age as modifiers of dose response, although it did indicate that at least one of the two variables was needed. This lack of discrimination held even though ERR_{1Sv} for $a < 35$ was a clear outlier to expression of ERR_{1Sv} as proportional to a power function of a (Fig. 4, left-hand panel). The analyses of Fig. 5 and Table 4 suggest that, for women under 20 years of age ATB, the ''early-onset'' contrast describes virtually all of the variability of ERR_{1Sv} by attained age, and that among all women there is little age-related variation to explain after adjustment for that contrast and age ATB. The same general result was found for parallel analyses of LSS breast cancer data from the present study using more restrictive criteria for the inclusion of cases and from the 1950–1985 series (*4*), more recent RERF Tumor Registry data (*20*), and the 1958–1987 LSS Tumor Registry report (*12*). [The 1958–1987 tumor registry data set used here, unlike that used in ref. (*12*), was stratified by attained age and included eight cases with estimated doses greater than 4 Gy.]

A virtue of the isotonic regression approach is that it can ''allow the data to tell us what is going on'' to a greater extent than with a more structured regression approach (e.g. linearity or log-linearity in ERR_{1Sv} with increasing age). The approach would have detected the ''early-onset'' phenomenon if it had been applied to earlier series. Another example is that major changes in ERR_{1SV} with increasing age ATB around 20 and 40 roughly coincide with the beginning of childbearing and the approach of menopause, respectively. The questions raised by these findings cannot be resolved at present, but they provide motivation for more probing studies.

The higher dose-specific ERR among women exposed before age 20 could reflect a lesser susceptibility to radiation carcinogenesis of terminally differentiated than undifferentiated breast cells, and a greater proportion of terminally differentiated cells among older women who would have been more likely to have experienced a full-term pregnancy before exposure. Russo and others (*31*) have shown that differentiated breast cells are less susceptible to cancer initiation by chemical carcinogens, for example. It is also conceivable that birth-cohort differences in reproductive history after 1945 may have influenced the likelihood that radiation-related DNA damage from the bombings would contribute to breast carcinogenesis. Experimental work by Clifton and others (*32, 33*) suggests that terminal differentiation of mammary cells after exposure to a carcinogen can reduce the carcinogenic potential of such cells.

In an earlier case–control study, we confirmed that early age at first full-term pregnancy, multiple births, and lengthy total lactation history were all protective against breast cancer among A-bomb survivors (*34*) and found that these factors were also protective against radiation-related breast cancer in particular, especially among women under 20 years of age ATB (*35*). The null hypothesis of an additive interaction between radiation dose and age at first full-term pregnancy was rejected ($P = 0.0035$) in favor of a more synergistic interaction, and in fact the evidence tended to favor a synergistic relationship somewhat stronger than the multiplicative interaction model: $P = 0.16$ for all women and $P = 0.08$ for women under 20 years of age ATB (*35*). Unpublished data from that study (C. Land, personal communication) show that on average among breast cancer controls, age at first full-term pregnancy was older (mean 24.8 compared to 23.8, $P = 0.02$), number of births was fewer (2.0 compared to 3.1, $P < 0.001$), and cumulative history of lactation was shorter (1.3 compared to 2.5 years, $P < 0.001$) for women under 20 ATB compared to older women. Thus another possibility is that dose-specific ERR was higher among women exposed before age 20 in part because their reproductive histories were in general less pro-

tective against both baseline and radiation-related breast cancer, and that this factor may have been somewhat more important for radiation-related risk than for baseline risk.

A larger case–control study, now possible given the increase in breast cancer cases over the past decade or so, could lead to useful new insights regarding the roles of age and reproductive history as modifiers of radiation-related breast cancer risk.

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